REMARKS

In order to simplify the issues, method claim 21 has been canceled and claims dependent thereon made dependent on claim 41.

The outstanding issues in this application are therefore:

1) whether the applicant was in possession of the invention at the time the application was filed;

2) whether the composition claims are obvious over either of the combinations of a) WO88/08708 and Conte, or b) Conte and Nordberg; and

3) whether the method claims are obvious over the combination of WO 88/08708, Conte and Riemann.

These will be considered in turn.

Possession of the invention

The applicants agree with the examiner that under current case law enablement and written description are distinct requirements of 35 USC 112 first paragraph and that recent case law has emphasized the need for possession of the invention at the time of filing. It should, however, be a very rare situation in which one skilled in the art has been able to write down his or her invention describing all that is set out in the claim in a way that it was enabled and still fail the written description test. The classic example of an invention that was enabled but where the written description test was not satisfied is that cited in *Vas-Cath v. Mahurkar*, in its reference to *In re Albrecht* 168 USPQ 293 where the specification described esters having 3 to 12 methylene groups, which would clearly have enabled one skilled in the art to produce equivalent esters of 2 - 12 methylene groups, but the lack of any written description of esters of two methylene groups prevented the applicant from being able to make claim to such esters. The issue was whether the specification contained language referring to what was being claimed. That

is not the situation in the present case. What is being claimed with respect to the means of release is what was described. There is no difference in the language.

As set out in *Vas-Cath*, written description requirement is that the application "convey with reasonable clarity to those skilled in the art that as of the filing date sought he or she was in possession of the invention."

Invention has two parts: conception and reduction to practice. Filing a patent application is constructive reduction to practice. *In re Glass* 492F.2d1228 181 USPQ 31. The classic explanation of what is meant by "conception is set out in *Townsend v. Smith* 36 F2d 292 (CCPA, 1929).

> The conception of the invention consists in the complete performance of the mental part of the inventive art. All that remains to be accomplished in order to perfect the act or instrument belongs to the department of construction not invention. It is therefore the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention as it is thereafter to be applied in practice that constitutes an available conception within the meaning of the patent law.

In moving from conception to reduction to practice, the inventor is entitled to rely on the services of others who make non-inventive contributions. The courts have held that once conception has occurred, the inventor may make use of the services of others in perfecting his invention without losing his right to a patent. See for example *Central Soya v. Hormel* 205 USPQ 421 (WD Okla. 1979), aff'd 645 F.2d 847, 209 USPQ 915 (10th Circuit 1981). As noted by the leading text Chisum on Patents,

> a disclosed conception is complete if a worker of ordinary skill can convert it into a working condition. (opening sentence of Section 10.04[3]).

That is precisely the situation in the present case. The specification gives references to ways in which to carry out these routine steps. A copy of the

Johnson chapter was submitted with the previous response and the examiner has clearly read the Conte article also cited in the application as filed Both of these were expressly incorporated by reference in the original application.(see page 7. three lines from the bottom of the page) Moreover, the art is replete with other such references showing the common knowledge of those skilled in the art to produce the claimed composition or carry out the claimed methods. Submitted herewith are copies of

Remington, The Science and Practice of Pharmacy (21st Edition, 2006) pages 939 - 964.;

Modern Pharmaceutics (2nd Edition) 1990, Chapter 16 "Sustained and Controlled-Release Drug Delivery Systems" pages 635 -671 and the front pages (including abstracts) of the following US patents:

5462747
5376384
5472708
5445829

5051261
5055306
5057317
5068111
5091189
5162117
5427799
5407687
5283065
4252786
4140756
4193985
4173626
4138475

Although the chapter from Remington was not published until after the effective date of the present application, it sets out clearly the historical background of different types of drug release formulations over time, making it clear that those skilled in the art had developed different types of delayed release compositions well before the filing of the

present application. Most of the references cited, other than those in the final section relating to "Novel Delivery Systems" were published in 1997 or earlier. The chapter therefore provides good information as to the tools normally available as part of the common knowledge of those skilled in the art at the time of filing the present application. The chapter from Modern Pharmaceutics sets out the position at about the time of filing the present application.

The patents describe a variety of techniques for achieving delayed release; note in particular that the abstracts of patents 5472708 and 5376384 specifically refer to controlling the timing of release.

The common general knowledge of one skilled in the art clearly shows that there was no inventive contribution required to go from what is set out in the present application to a manufactured product. Conception was complete at the time of filing the application and the applicant was therefore in possession of the invention at that time.

While, as noted by the Examiner there are situations in which something may be enabled and not described (as is the case in In re Albrecht noted above), this is not one of those cases. The invention in the present case is the composition and method set out in the claims. A verbal description is given of both composition and method. All that is required to convert that description into an actual composition that can be taken or a method in which the composition is taken is a matter of routine implementation by those skilled in the art. Suitable excipients and extended release coatings were well known. There is no need for the applicant to set out information that was common knowledge to the skilled worker, the intended reader of the application. It is therefore submitted that on a true understanding of what is meant by "possession of the invention" (i.e. complete conception as judged by the standard case law on the subject) the requirements of 25 USC 112 for a written description have been clearly met.

Turning now to the questions of obviousness, the Supreme Court has pointed out that:

> [R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR International Co. v. Teleflex, Inc.* 550 U.S. 398 82 USPQ2d 1385 (2007) .

It is submitted that there is no such rational underpinning in any of the arguments set forth by the Examiner against the claims now in this application.

We deal first with the alleged obviousness of the composition claims over the combination of WO88/08708 and Conte. There are two key passages in the Examiner's argument. The first is

> The skilled artisan would have been motivated [to formulate galanthamine or galanthamine-like analogs into compositions providing delayed release] because Conte et al teach that psychotropic active drugs are agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes in circadian rhythmicity ...

However, cholinesterase inhibitors were not considered conventional psychotropic drugs by Conte. As discussed in the previous response, one cannot simply classify Alzheimer's drugs with the broad class of psychotropic drugs. The Examiner rejects this argument on the basis that some others have referred to "cholinergic compounds" as "unique psychotropic agents". If they are unique, it would seem that more is required than mere assertion to justify concluding that Conte's passing reference to psychotropic drug as applying to them. In any case, nothing in Conte points towards formulating any drug to delay its release for the purpose of avoiding activity at a particular time rather than promoting activity at a desired time.

The second key point in the Examiner's argument is

> One of ordinary skill in the art would recognize that a patient with Alzheimer's disease would not be in need of medication while sleeping.

This is clearly wrong. As discussed in detail in response to the previous action, the most commonly used drug for treatment of Alzheimer's disease continues to be administered in formulations that are active during sleep and at the time of the present invention, the general consensus was that one should not vary the dosage level of Alzheimer's drugs between the day and night.. The art affirmatively chose to medicate AD patients during sleep. Fluctuations in the level of acetylcholinesterase inhibition were thought to be responsible for nausea and vomiting, the leading side effects and reason for discontinuing the cholinesterase inhibitors. The good tolerability of drugs that acted throughout the 24 hour period was attributed to their irreversibility or very long half life, and a shorter-acting cholinesterase inhibitor was recently reformulated into a 24 hour patch.

It is therefore submitted that the composition claims are not obvious over a combination of WO88/08708 and Conte.

So far as the second obviousness argument based on the combination of Conte and Nordberg is concerned, Nordberg simply discloses the possible use of rivastigmine rather than galanthamine for treatment of Alzheimer's disease. The Examiner's arguments seem to be the same as discussed above. It is submitted that they are wrong for the reasons discussed above.

The final issue for consideration is that of whether the combination of WO88/08708, Conte and Riemann makes the method claims obvious. The Examiner's position is that Riemann would give one skilled in the art

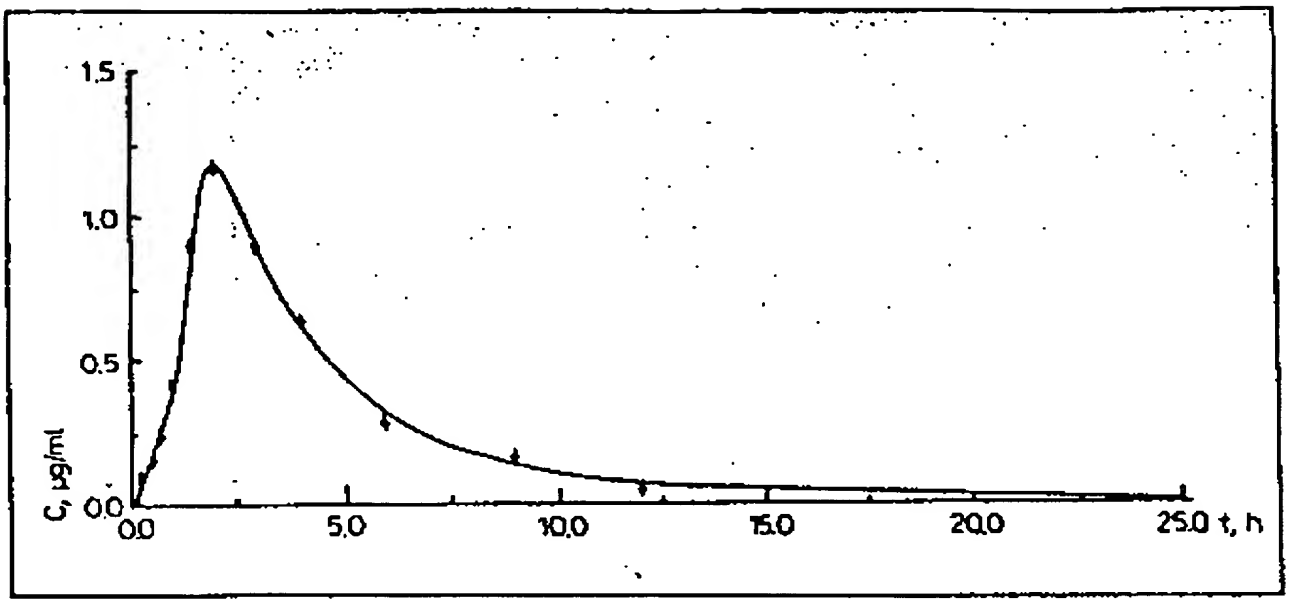
> at least a reasonable expectation that delaying the release of galanthamine or analogues thereof during periods of sleep would avoid waking a patient from sleep since no anticholinesterase activity would occur.

As noted above, at the time of the present application, the presumption was that one needed to maintain a constant level of acetylcholinesterase activity and not vary it with time. However, even if this had not been the case, Reimann would not have led one to seek to avoid acetylcholinesterease inhibition at during sleep. The Examiner's position is predicated on the assumption that Reimann would discourage the administration of galantamine during sleep. This is not the case.

In addition to reporting when galanthamine significantly disturbs sleep, Reimann reports when it does not.

The Reimann article discloses that galanthamine administered one hour before bedtime produces awakenings and disturbs sleep. It does so significantly during the first cycle of sleep stages, but not the second or third. A higher dose, 15 mg, produces more awakenings than 10 mg does. Neither dose, however, causes early morning awakening. It appears, then, that galanthamine's disturbance of sleep occurs when plasma levels are high due to recent administration, or to higher doses.

The time course of galanthamine plasma levels following the oral administration of 10 mg, as was done in the Reimann protocol, is shown in the figure below. This figure comes from Mihailova et al (1989) and is discussed in the introduction of the Reimann paper.



Reimann administered galanthamine one hour before lights out. Thus, the peak plasma galanthamine level which occurs two hours after oral ingestion occurred after one hour of sleep. Subsequently, plasma galanthamine levels decline substantially. The first sleep cycle was significantly affected during the night, but not the second or third. Apparently, the peak galanthamine level achieved after ingestion of 10 mg is able to disturb sleep significantly, but not subsequent levels. The same would be true for the 15 mg dose also used in the Reimann protocol. Thus, the galanthamine preparation which was available at the time of the Reimann study, an immediate-release formulation, would disturb sleep if given near to bedtime.

In addition to sleep disturbance, it was also thought that the varying levels of cholinesterase inhibition produced by preparations such as immediate-release galanthamine were the cause of nausea and vomiting and discontinuation of treatment (see prior response). The field was therefore motivated to produce dosage formulations which kept acetylcholinesterase inhibition, and consequently drug levels, constant.

Delivering the daily galanthamine dosage at a constant level over the course of a day would avoid the peaks of immediate release galanthamine. The recommended daily dose,

30 mg, (Dal Bianco 1991, Nordberg 1999) would then be released at 10 mg per 8 hours. Mihailova provides the area under the curve produced by 10 mg galanthamine as 5.38 μg.h/ml. This amount, provided uniformly over 8 hours, would produce a steady level of 0.67 μg/ml. This level is about half the peak level produced by an immediate release tablet.

Thus Reimann, in reporting when galanthamine did and did not significantly disturb sleep is helpful in the development of a galanthamine formulation with steady release over the course of a 24 hour day.

The invention as claimed is therefore not obvious and does comply with the requirements of 35 USC 103.

In view of the foregoing, it is submitted that this application should be allowed and an early action to this end is respectfully solicited.

Respectfully submitted,

JOHN RICHARDS
C/O LADAS & PARRY LLP
26 WEST 61 ST STREET
NEW YORK, NEW YORK 10023
REG. NO. 31053
TEL. NO. (212) 708-1915